

Moyamoya Disease, a Rare Cause of Recurrent Strokes in an African Sickle Cell Child: Does hydroxyurea have a Role in this Context?

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Abstract: *Background:* Neurological complications are a significant cause of morbidity and mortality in sickle cell patients with reported incidence of stroke in Africa as high as 1.3/100 patient per year [1,2]. There is an association between sickle cell disease (as well as other hemoglobinopathies) and Moyamoya disease [3]. Data on the occurrence of this condition in African sickle patient are scarce. Likewise the role of hydroxyurea among patients with both sickle cell anemia and Moyamoya disease in preventing stroke has not yet been studied in Africa.

Case presentation: In the present report, we describe an African child who had a recurrent stroke. She was later diagnosed as having Moyamoya disease while already receiving hydroxyurea.

Conclusion: Moyamoya disease is a rare condition associated with recurrent stroke in African sickle children. The role of hydroxyurea in this context is still unclear.

Keywords: Moyamoya sickle cell, stroke, hydroxyurea.

BACKGROUND

In the US, up to 43% of patients with sickle cell anemia (SCA) and strokes will develop Moyamoya-like collaterals on imaging studies [4]. Moyamoya disease is deemed a progressive steno-occlusive disease at terminal portions of the bilateral internal carotid arteries with the development of "Moyamoya vessels" as collateral channels of circulation [5, 6]. Sickle cell patients with moyamoya have a 5-fold increase chances for recurrent stroke and more neurophysiological deficit [7] than to those without evidence of collateral vessels [4]. There is an association between sickle cell disease (as well as other hemoglobinopathies) and moyamoya disease [3]. Dobson *et al.* [7] reported that that up to 41% of patients with sickle cell disease experience recurrent cerebral vascular accidents (CVA) after an initial stroke despite chronic transfusions and that the risk of recurrence is significantly higher for those who have moyamoya collaterals. HU may reduce CVA attack in patients with SCA [8-10]. In a Brazilian study, three patients received hydroxyurea therapy for a mean follow-up of 70.3 months and there was no recurrence of stroke [8]. A similar 100% positive response was reported in the Venezuela. However there are no larger series or randomized controlled trial has reported on the efficacy of hydroxyurea as the sole therapeutic

strategy after a stroke [8]. We also do not know whether this positive effect is also seen in those with both SCA and moyamoya. Current findings from the Stroke With Transfusions Changing to Hydroxyurea (SWITCH) [11], trial that hydroxyurea with regular phlebotomy was unlikely to prevent recurrent strokes better than standard therapy combining blood transfusion with deferasirox, have brought conflicting evidence regarding the positive role of this drug in SCA.

CASE PRESENTATION

Clinical Evaluation and Lines of Investigations

A 12- year -old female child with SCA was readmitted (2011) in medical ward with low grade fever, dry cough and vomiting for two days prior to admission. Eighteen hours later she developed generalized tonic clonic seizures. The seizure lasted approximately 30 seconds, repeating after 5 minutes. She did not have associated bowel or bladder incontinence or tongue or cheek biting during the seizure.

The patient's complex medical history included diagnosis of sickle cell anemia at the age of 18 months (2001) which was associated with normal growth and development until the age of six years. In 2006, she suffered stroke for the first time which was characterized by weakness of the right arm and leg. This was followed by another stroke in 2008 which was characterized with left arm weakness. In 2009 she had another episode of stroke leaving her with bilateral leg

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weakness and another episode in 2010 which was characterized with expressive dysphasia. During these episodes the patient was treated palliatively in both general ward and intensive care unit and she received irregular blood transfusion (6 times).

The patient's routine/ regular home medications included folic acid, junior aspirin, and hydroxyurea which was started since 2009. She had no known drug allergies. There was no family history of sickle cell anemia, stroke or seizures. Socially, the patient was in standard IV primary school and lived with her parents.

On physical examination, the patient was awake, alert, and oriented to person, place, and time. She was stunted /height 136cm which is below – 2 standard deviation of her expected height. She was pale and jaundiced. She had bossing of the skull. Vital signs (blood pressure, 110/80 mm Hg; body temperature 38.1⁰C, heart rate 86 beats per min were normal. Head and neck were unremarkable. The respiratory examinations revealed features of consolidation and oxygen saturation of 98% on room air. She was paraplegic and wheelchair-bound with dysphasia.

Results of a complete blood cell count showed mild normocytic anemia with normal leukocyte and platelet counts and the peripheral smear revealed Sickle cells, polychromasia and a few nucleated cells. Blood slide for malaria parasite and urine culture were negative. Urinalysis was normal. High performance liquid chromatography showed S-window of 82%. Metabolic panel showed slightly raised indirect bilirubin with normal renal profiles. Coagulation studies were within normal limits, and hypercoagulable workup was not done as it

was unavailable. Other diagnostic studies included a chest radiograph which showed consolidation in right middle lobe and an electrocardiogram, which showed sinus tachycardia at 115 beats per minute. Transcranial doppler ultrasound (Figure 1) showed low cerebral blood flow velocities i.e. <50cm/sec and Computerized Tomography (CT) scan showed brain atrophy. Intracranial magnetic resonance angiogram (MRA) done in India in 2009 revealed narrowing of the right internal carotid artery and supraclenoid part of the left internal carotid artery (Figure 2). There was stenosis of right middle cerebral artery and of proximal left middle cerebral artery with multiple dilated distal collateral, findings suggestive of Moyamoya disease.

DISCUSSION

We discuss an African child who has been suffering from various complications of sickle cell anemia such as recurrent strokes and anemia requiring blood transfusion. In Tanzania, this is a first reported case of sickle cell anaemia with recurrent stroke despite being on hydroxyurea. The patient reported here is unusual for several reasons. First, the association of SCA and Moyamoya disease is rare and, to our knowledge, has never been reported in African setting. Second, the role of hydroxyurea treatment in sickle cell anemia with Moyamoya syndrome is unknown. Moyamoya disease is especially rare in children of African origin. Uchino *et al.* [12] found only 27 African Americans with Moyamoya disease, 13 of whom had sickle cell disease and were thus classified as having moyamoya syndrome. In addition, African Americans were found to have a median disease onset age of 18 years. As noted

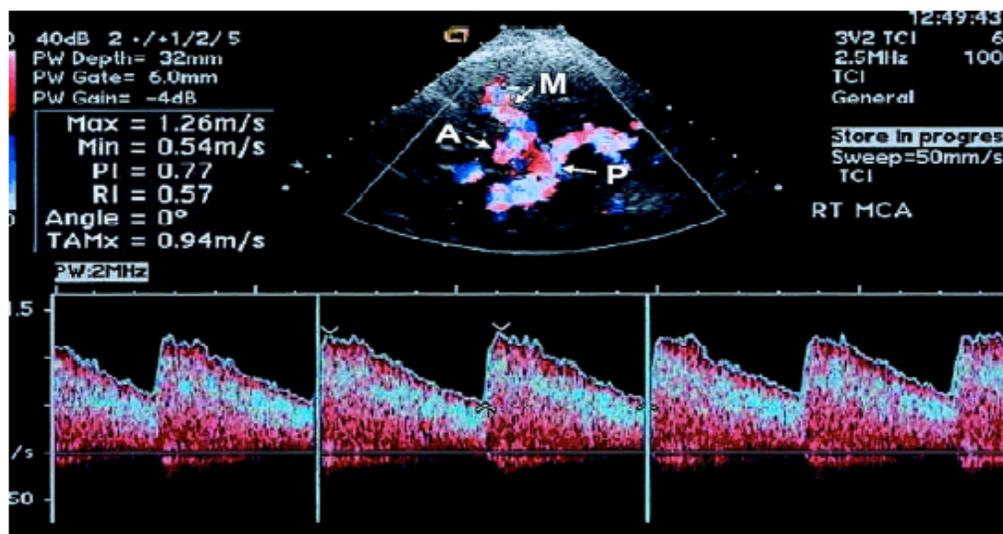


Figure 1: Trans cranial Doppler results showing low cerebral blood flow velocities i.e. <50cm/sec.

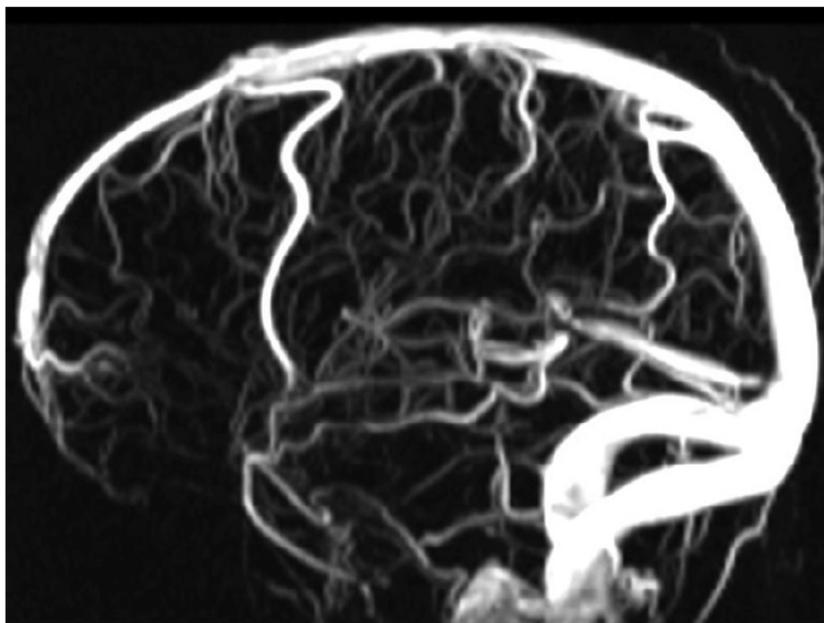


Figure 2: A magnetic resonance image (MRI) of the brain with and without gadolinium contrast showing narrowing of the right internal carotid artery and supraclenoid part of the left internal carotid artery. There is also stenosis of right middle cerebral artery and of proximal left middle cerebral artery with multiple dilated distal collateral.

earlier, the patient described in the present report was diagnosed much earlier-at the age of 9 years. Chiu *et al.* [13] also found the clinical expression of Moyamoya disease to be different in the United States compared to Asia. They did not find a bimodal age distribution seen among Asian patients, as the average age of diagnosis was 32 years. The incidence peaks in two age groups in the Asian patients [14]: children who are approximately 5 years of age and adults in their mid40s. However, epidemiology may be influenced by two factors: (1) patients of Asian origin may have an increased tendency to be diagnosed as having Moyamoya, and (2) patients presenting with strokes at relatively young ages are more likely to have an aggressive workup, which may lead to a greater sensitivity in the diagnosis of Moyamoya disease [12].

This African child was started on hydroxyurea in 2009 having suffered three strokes. Despite being on hydroxyurea for a year, she again suffered another stroke and seizures. Hydroxyurea has been reported to be effective in improving survival and reducing morbidity in some sickle cell patients with reduction in frequency of painful episodes, and hospital admissions [15]. Earlier studies found had reported that HU is also effective in the prevention of brain injury due to cerebrovascular disease [16]. Abraham S *et al.* [8] in the US studied five children with SCA who had suffered stroke, in three of them after a first episode and in the other two after a second CVA. Four patients took HU at

a dose of 40 mg/kg/d, one patient at 30 mg/kg/d and they found none of the patients had recurrent stroke during 42–112 months of observation implying that HU might have prevented recurrence of stroke in SCA. However, current studies [9,10] have shown that short and long-term hydroxyurea treatment reduced but did not eliminate the risk of stroke recurrence. This child received hydroxyurea for a year before experiencing another attack of stroke and seizures. Chronic transfusions are effective in preventing the recurrence of infarctive strokes in patients with sickle cell disease [17]. The reasons why some patients develop recurrences [18] while complying with transfusions are unknown. The development of Moyamoya disease in some sickle cell patients like this child might contribute to recurrence of stroke. However further studies are needed to establish the role of hydroxyurea in preventing recurrent stroke in patients not only with SCA but also with Moyamoya disease. In this child, hydroxyurea did not appear to be helpful in preventing further strokes.

CONCLUSIONS

Moyamoya disease appears to be an extremely rare condition associated with recurrent stroke among African sickle children but should be considered in those with recurrent strokes. The role of hydroxyurea in preventing strokes among children with both SCA and Moyamoya diseases remains in a gray zone.

CONSENT

Written informed consent was obtained from the parents of the child for publication of this case report.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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REFERENCES

- [1] Izuora GI, Kaine WN, Emodi I. Neurological disorders in Nigerian children with homozygous sickle cell anaemia. *East Afr Med J* 1989; 66: 653-57.
- [2] Amayo EO, Owade JN, Aluoch JR, Njeru EK. Neurological complications of sickle cell anaemia at KNH: a five year retrospective study. *East Afr Med J* 1992; 69: 660-62.
- [3] Fryer RH, Chiriboga CA, Feldstein NA. Sickle cell anemia with moyamoya disease. outcome after EDAS procedure. *Paediatr Neurol* 2003; 29: 124-30. [http://dx.doi.org/10.1016/S0887-8994\(03\)00047-X](http://dx.doi.org/10.1016/S0887-8994(03)00047-X)
- [4] Smith ER, McClain CD, Heeney M, Scott RM. Pial synangiosis in patients with moyamoya syndrome and sickle cell anemia: perioperative management and surgical outcome. *Neurosurg Focus* 2009; 26(4): E10. <http://dx.doi.org/10.3171/2009.01.FOCUS08307>
- [5] Kawamura K, Cheng Y, Kawamura N, *et al.* Moyamoya disease In *Handbook of Clinical Neurology*. Vol 2. Amsterdam, The Netherlands: Elsevier 1989; pp. 293-306.
- [6] Kikuta K, Miyamoto S, Kataoka H, *et al.* An adult case of moyamoya syndrome that developed dural sinus thrombosis associated with protein C deficiency: a case report and literature review. *Surg Neurol* 2005; 63: 480-84. <http://dx.doi.org/10.1016/j.surneu.2004.04.027>
- [7] Dobson SR, Holden KR, Nietert PJ, Cure JK, Laver JH, Abboud MR. Moyamoya syndrome in childhood sickle cell disease: a predictive factor for recurrent cerebrovascular events. *Blood* 2002; 99(9): 3144-50. <http://dx.doi.org/10.1182/blood.V99.9.3144>
- [8] Sumoza A, Renate B, Sumoza D, Fairbank V. Hydroxyurea (HU) for Prevention of Recurrent Stroke in Sickle Cell Anemia. *Am J Hematol* 2002; 71: 161-65. <http://dx.doi.org/10.1002/ajh.10205>
- [9] Greenway A, Russell E, Courtney DT. Long-term results using hydroxyurea/phlebotomy for reducing secondary stroke risk in children with sickle cell anemia and iron overload. *Am J Hematol* 2011; 86: 357-61.
- [10] Ware RE, Zimmerman SA, Sylvestre PB. Prevention of secondary stroke and resolution of transfusional iron overload in children with sickle cell anemia using hydroxyurea and phlebotomy. *J Pediatr* 2004; 145: 346-52. <http://dx.doi.org/10.1016/j.jpeds.2004.04.058>
- [11] Ware RE, Helms RW. Stroke With Transfusions Changing to Hydroxyurea (SWITCH). *Blood* 2012; 119: 3925-32. <http://dx.doi.org/10.1182/blood-2011-11-392340>
- [12] Uchino K, Johnston SC, Becker KJ, Tirschwell DL. Moyamoya disease in Washington State and California. *Neurology* 2005; 65: 956-58. <http://dx.doi.org/10.1212/01.wnl.0000176066.33797.82>
- [13] Chiu D, Shedden P, Bratina P, Grotta JC. Clinical features of moyamoya disease in the United States. *Stroke* 1998; 29: 1347-51. <http://dx.doi.org/10.1161/01.STR.29.7.1347>
- [14] Baba T, Houkin K, Kuroda S. Novel epidemiological features of moyamoya disease. *J Neurol Neurosurg Psychiatry* 2008; 79: 900-4. <http://dx.doi.org/10.1136/jnnp.2007.130666>
- [15] Charache S, Terrin ML, Moore RD, *et al.* Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. *N Engl J Med* 1995; 332(20): 1317-22. <http://dx.doi.org/10.1056/NEJM199505183322001>
- [16] Ware RE, Steinberg MH, Kinney TR. Hydroxyurea: an alternative to transfusion therapy for stroke in sickle cell anemia. *Am J Hematol* 1995; 50(2): 140-3. <http://dx.doi.org/10.1002/ajh.2830500211>
- [17] Pavlakis SG, Prohovnikl PS, DeVivo DC. Neurologic complications of sickle cell disease. *Adv Pediatr* 1989; 36: 247-76.
- [18] Wang SC, Hong JH, Hsueh C, Chiang CS. High risk of recurrent stroke after discontinuance of five to twelve years of transfusion therapy in patients with sickle cell disease. *J Pediatr* 1991; 118: 377-82.

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